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REVIEW ARTICLE

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Dental implants in patients with head and neck cancer—A systematic review and meta-analysis of the influence of radiotherapy on implant survival

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Abstract

Purpose: The purpose of this meta-analysis was to compare implant survival in irradiated and non-irradiated bone and to investigate potential risk factors for implant therapy in oral cancer patients.

Material and methods: An extensive search in the electronic databases of the National Library of Medicine was performed. Systematic review and meta-analysis were conducted according to PRISMA statement. The meta-analysis was performed for studies with a mean follow-up of at least three and five years, respectively.

Results: The systematic review resulted in a mean overall implant survival of 87.8% (34%–100%). The meta-analysis revealed a significantly higher rate of implant failure in irradiated bone compared to non-irradiated bone ($p < .00001$, OR 1.97, CI [1.63, 2.37]). The studies also showed that implants placed into irradiated grafted bone were more likely to fail than those in irradiated native bone ($p < .0001$, OR 2.26, CI [1.50, 3.40]).

Conclusion: Even though overall implant survival was high, radiotherapy proves to be a significant risk factor for implant loss. Augmentation procedures may also increase the risk of an adverse outcome, especially in combination with radiotherapy.

Clinical relevance: The treatment of patients receiving radiotherapy of any form requires precise individual planning and a close aftercare. Implants should be placed in local bone rather than in bone grafts, if possible.

KEYWORDS

bone grafts, dental implants, head and neck cancer, radiation therapy, survival rate

1 | INTRODUCTION

Dental rehabilitation of patients treated for cancer of the head and neck region is an important but challenging task. Oral cancer is a common disease which has affected about 14.7 of 100,000 people in Germany in the year 2017 (Koch-Institut, Z.f.K.i.R, 2021). In view of the poor 5-year survival of only about 50% (Koch-Institut, Z.f.K.i.R, 2021), an early and efficient treatment is indispensable.

Such treatment often includes radiotherapy alongside surgery and chemotherapy (AWMF, 2021; Wierzbicka & Napierala, 2017). Ablative surgery, as well as removal of dental foci in preparation for primary radiotherapy, can lead to limiting defects, accompanied by a loss of masticatory function and a lower quality of life (AWMF, 2021; Wijbenga et al., 2016). As a result, dental rehabilitation is often urgently needed (Batstone, 2018). Due to altered anatomy after resection, implant placement may be difficult to perform (Petrovic et al., 2019). For those patients who underwent radiotherapy, the short- and long-term effects of radiation represent a further factors influencing the implant survival and the success of the prosthodontic supra-construction. The early consequences of irradiation include decreased cell proliferation and damage in the bony remodelling system (Costa & Reagan, 2019; Tanaka et al., 2013). Increased osteoclast activity and latent decreased osteoblast activity lead to a loss of bone quantity and quality (Costa & Reagan, 2019). Furthermore, radiotherapy causes hyperemia, endarteritis, thrombosis, cell loss, hypovascularity and fibrosis (Curi et al., 2016; Marx & Johnson, 1987). Moreover, acute inflammation can be triggered by increased inflammatory cytokines (Costa & Reagan, 2019). As a long-term effect, the bone shows a reduced healing capacity due to reduced blood supply and hypocellularity of the bone marrow in combination with infiltration of adipocytes and fibroatrophy (Costa & Reagan, 2019; Delanian & Lefaix, 2004;Petrovic et al., 2019; Tanaka et al., 2013). A severe complication is the osteoradionecrosis (ORN) of the jaw (Petrovic et al., 2019; Tanaka et al., 2013).

Despite the above-mentioned limitations, oral implants can provide a great benefit, especially through an improvement of retention and mastication (Buurman et al., 2013; Korfage et al., 2014). This may be important as patients treated with radiotherapy often suffer from xerostomia (Tanaka et al., 2013), which has a negative effect on the retention and fitting of conventional removable overdenture (Batstone, 2018; Chambers et al., 2004). As a matter of fact, in 2015, the German guideline for oral rehabilitation in irradiated patients concluded that dental implants should be considered for those patients in view of good long-term results and improvement of oral health-related quality of life. For patients who underwent bony reconstruction, radiotherapy was found to be a great risk factor for implant loss, resulting in a significant lower implant survival (AWMF, 2015). This study is intended to help update this guideline taking currently published literature into account.

2 | MATERIAL AND METHODS

2.1 | Protocol development and eligibility criteria

The development of the study protocol was complying to the *Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)*. The systematic review was not registered retrospectively on PROSPERO. The focussed question of the evaluation was worked out in the *Patient*, *Intervention*, *Comparison and Outcome (PICO)* format and can be specified as 'Is there a difference between implant survival in irradiated jaw and non-irradiated jaw?'

- Population: Patients with cancer of the head and neck region rehabilitated with dental implants
- Intervention: Radiotherapy of the head and neck (before and/or after implant placement)
- Comparison: Non-irradiated patients
- Outcome: Implant survival

2.2 | Inclusion criteria

Randomized controlled trials, prospective clinical trials and retrospective studies were included in this study if they provided information about the survival of dental implants in irradiated head and neck cancer patients.

The following detailed criteria had to be met:

1. Inclusion of more than ten irradiated subjects
2. Study published in English or German
3. Prospective studies: randomized controlled, non-randomized-controlled, cohort studies
4. Retrospective studies: controlled, case–control, 'single cohort'
5. For meta-analysis: studies with a follow-up of at least three or five years, respectively

If a study did not meet all the criteria listed above or important information was missing and could not be provided, it was excluded from the evaluation. Another criterion for exclusion was the use of replacement implants after implant loss if they were included into the evaluation of the overall implant survival rate.

2.3 | Search strategy

This research is based on a previous comprehensive literature review by Schiegnitz et al. (2014), which evaluated articles published between January 1990 and January 2013. To obtain up-to-date information, the electronic databases of the National Library of Medicine were investigated for articles that were published in the period from February 2013 to February 2021 using the MeSH Terms (medical subject heading):

((((((dental implants[MeSH Terms]) OR (dental implantation[MeSH Terms])) OR (oral rehabilitation[MeSH Terms])) OR (dental prostheses, implant supported[MeSH Terms])) OR (osseointegrated implants[MeSH Terms])) OR (implant supported overdenture[MeSH Terms])) AND ((((((((((head and neck cancer[MeSH Terms]) OR (head and neck neoplasms[MeSH Terms])) OR (head and neck neoplasms/radiotherapy[MeSH Terms])) OR (oral cancer[MeSH Terms])) OR (ablative surgery[MeSH Terms])) OR (irradiated jaw[MeSH Terms])) OR (irradiated bone graft[MeSH Terms])) OR (squamous cell carcinoma[MeSH

Terms])) OR (radiation[MeSH Terms])) OR (radiotherapy[MeSH Terms])) OR (bony reconstruction[MeSH Terms])) (15.04.2021. 20:00)

This was completed by manually research on the keywords 'dental implants' and 'irradiated patients'. In addition, the reference lists of other meta-analyses, publications and reviews with similar interest were screened. Furthermore, the Cochrane library was investigated for reviews and studies published on this subject.

2.4 | Study selection

At first, the electronic database of the National Library of Medicine was screened for relevant publications, which were assessed by their title and abstract. All studies that met the mentioned inclusion criteria were evaluated more precisely. To do so, full-text articles were procured, and authors were contacted in case of any ambiguities or missing information. The PRISMA flow diagram (Figure 1) reports the number of identified, excluded and included studies of this review and visualizes the flow of information through the different phases.

2.5 | Risk of bias evaluation

An analysis of the studies' risk of bias was conducted using the New Caste Ottawa Scale for studies comparing irradiated and non-irradiated patients. If the study was missing a non-irradiated control group, the risk of bias assessment was performed following Moga et al. (2012). In addition, the overall level of evidence was assessed using the GRADE classification. (Cochrane Deutschland, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften – Institut für Medizinisches Wissensmanagement, 2016)

2.6 | Statistical analysis

The software package RevMan (Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020) was used for the meta-analysis. With the help of this program, the collected data were evaluated, and the overall effects were estimated. If p was <.05, the result was considered statistically significant. Furthermore, forest plot and funnel plot were produced (Figures 2–9).

3 | RESULTS

3.1 | Study selection and results of quality assessment of selected studies

Altogether, the currently conducted literature research resulted in 502 studies, of which 58 abstracts were screened and full-text documents were procured. After further exclusion of 28 studies for different reasons and adding four studies that were identified through manual research, 29 studies were finally selected. These studies were complemented by the 30 studies identified in the previous research. Table 1 summarises the results of all 59 studies that were evaluated within the framework of this study.

The meta-analysis was conducted including the results of the research previously performed by Schiegnitz et al. (2014) to provide information about the influence of radiotherapy on implant survival taking into account studies published from 1990 to 2021. Of overall 19 studies from the period of 2013 to 2021 comparing implant survival in irradiated and non-irradiated bone, eleven and six had a follow-up of at least three and five years, respectively. These were included in the meta-analysis as well as ten studies from the previous analysis. Regarding the influence of the type of bone, a comparison of implant survival in irradiated grafted versus irradiated local bone with a follow-up of at least 36 and 60 months was performed including nine and six studies, respectively. This included data from five newly identified publications with a follow-up of at least 36 months and three with a follow-up of at least 60 months. The term grafted bone refers to vascularised or non-vascularised autologous bone grafts, such as free fibula or iliac crest flaps.

However, 18 studies investigated in the current literature research were not used for meta-analysis. Besides the reasoning of too short of a follow-up (Alberga et al., 2020; Burgess et al., 2017; Ch'ng et al., 2016; Gander et al., 2014; Hessling et al., 2015; Moore et al., 2019; Pompa et al., 2015; Woods et al., 2019), the second reason for exclusion was that the studies only assessed implants placed in irradiated bone, which means they were lacking a non-irradiated control group (Buurman et al., 2013; Curi et al., 2018; Di Carlo et al., 2019; Nack et al., 2015; Neckel et al., 2020; Papi et al., 2019; Rana et al., 2016; Sandoval et al., 2020). Ettl et al. (2020) were reporting implant success using a modified version of the Albrektsson criteria (Albrektsson et al., 1986), and their study was therefore excluded. In the study from Dholam et al. (2013), overall implant success was given as well as the rate of osseointegration. As it cannot be said with certainty that the rate of osseointegration is consistent with the implant survival rate, those values were excluded precautionary. Nevertheless, even within the studies included in the meta-analysis, there are still differences in the way implant survival is determined or defined.

3.2 | Risk of bias evaluation

For studies comparing the outcome of implants in irradiated and non-irradiated bone, the Newcastle-Ottawa scale was used to evaluate the risk of bias. The results are shown in Table 2.

To evaluate the risk of bias of studies without a non-irradiated control group, the following four questions were addressed following Moga et al. (2012).

1. Were the cases adequately described? (Selection)
2. Intervention: Has the intervention been adequately described and has the relevant data been adequately collected?

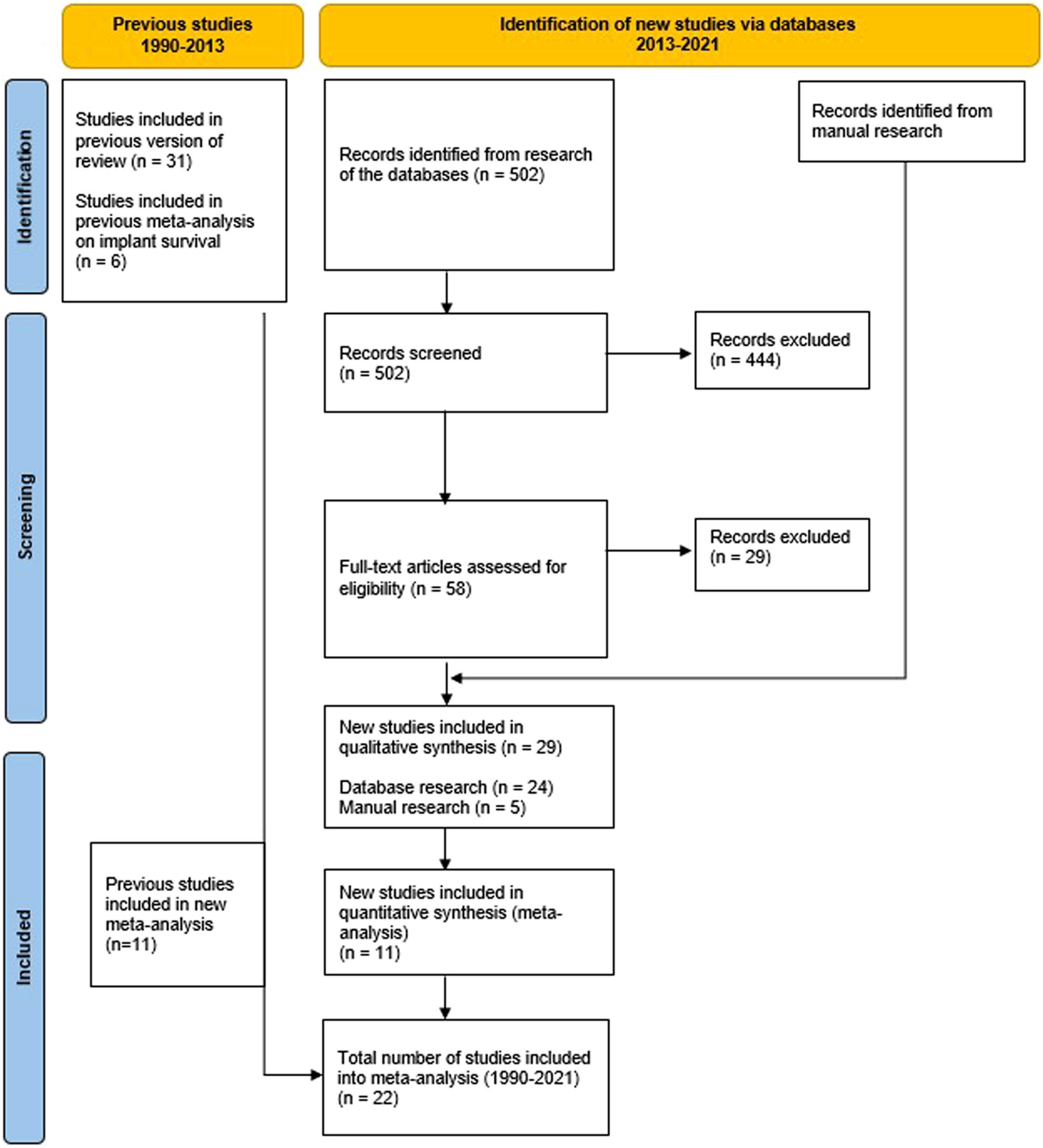


FIGURE 1 PRISMA flow diagram

3. Has the outcome been adequately described, and the corresponding data adequately collected?
4. Was follow-up long enough for outcomes to occur?

This analysis can be seen in Table 3. In addition, evidence levels were assigned to the individual studies. The classification was made according to study type and quality.

- IIb: prospective cohort study (RT vs NRT)
- IIIb: retrospective cohort study (RT vs NRT)
- IV: case series (RT) and poor-quality cohort study (RT vs NRT)

According to GRADE, the overall evidence regarding the outcome implant survival is rated as low. The grading of the significance was due to the lack of comparability of the patient groups, missing information

Study or Subgroup	Irradiated Events	Irradiated Total	Non-irradiated Events	Non-irradiated Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Schliephake 1999	73	145	112	264	19.0%	1.38 [0.92, 2.07]	1999
Weischer 1999	10	83	5	92	2.0%	2.38 [0.78, 7.29]	1999
Werkmeister 1999	8	30	19	79	3.7%	1.15 [0.44, 3.00]	1999
Cao 2003	18	53	11	78	2.8%	3.13 [1.33, 7.36]	2003
Granström 2005	147	631	76	614	28.5%	2.15 [1.59, 2.91]	2005
Yerit 2006	43	154	4	84	1.8%	7.75 [2.67, 22.45]	2006
Klein 2009	13	116	12	74	6.3%	0.65 [0.28, 1.52]	2009
Korfage 2010	13	123	1	72	0.5%	8.39 [1.07, 65.55]	2010
Salinas 2010	23	90	8	116	2.5%	4.63 [1.96, 10.95]	2010
Linsen 2012	8	127	6	135	2.6%	1.45 [0.49, 4.29]	2012
Fierz 2013	14	62	4	42	1.8%	2.77 [0.84, 9.11]	2013
Jacobsen 2014	14	47	13	93	3.0%	2.61 [1.11, 6.15]	2014
Korfage 2014	31	318	5	206	2.6%	4.34 [1.66, 11.36]	2014
Doll 2015	30	292	35	538	10.7%	1.65 [0.99, 2.74]	2015
Hakim 2015	5	48	4	71	1.4%	1.95 [0.50, 7.66]	2015
Barber 2016	4	25	6	57	1.5%	1.62 [0.41, 6.33]	2016
Ernst 2016	3	88	1	106	0.4%	3.71 [0.38, 36.27]	2016
Flores-Ruiz 2018	11	78	2	28	1.2%	2.13 [0.44, 10.29]	2018
Laverty 2019	26	525	8	254	4.9%	1.60 [0.71, 3.59]	2019
Patel 2020	4	121	5	241	1.6%	1.61 [0.43, 6.12]	2020
Pieralli 2021	2	113	2	104	1.0%	0.92 [0.13, 6.64]	2021
Total (95% CI)		**3269**		**3348**	**100.0%**	**2.06 [1.75, 2.42]**	
Total events	500		339				

Heterogeneity: Chi² = 30.05, df = 20 (P = 0.07); I² = 33%
Test for overall effect: Z = 8.68 (P < 0.00001)

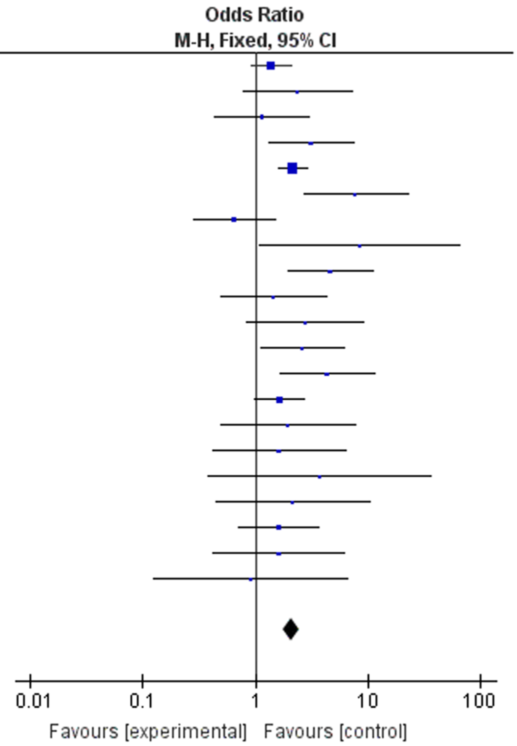


FIGURE 2 Forest plot of implant failure in irradiated versus non-irradiated bone (control) for studies with follow-up ≥36 months (literature, 1990–2021)

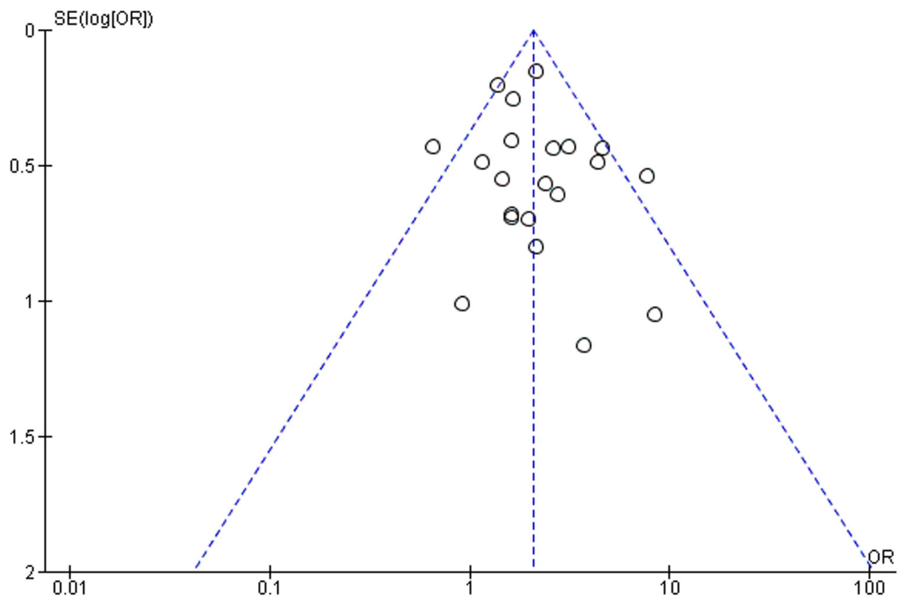


FIGURE 3 Funnel plot of analysis shown in Figure 2

in many cases and inconsistency of the results. In addition, the studies were very heterogeneous, especially with regard to the selection of patients and the definition and evaluation of the results.

3.3 | Study characteristics of the newly identified studies from February 2013 to 2021

In total, 6645 dental implants placed in 1633 patients were included in this review of the literature from 2013 to 2021. Thereof, 4031 implants were inserted into irradiated bone. The non-irradiated control group received 2614 implants. It has to be mentioned that those numbers do not include the entirety of the 17 patients with 84 implants in irradiated bone assessed in the study by Di Carlo et al. (2019) as the patient data partially match those from Pompa et al. (2015). The number of patients with dental implants ranged from 10 (Sandoval et al., 2020) to 246 (Ch'ng et al., 2016). In addition, large differences regarding the follow-up were observed, as the mean follow-up ranged from only 7 months (Sandoval et al., 2020) up to 121 months Doll et al. (2015). In

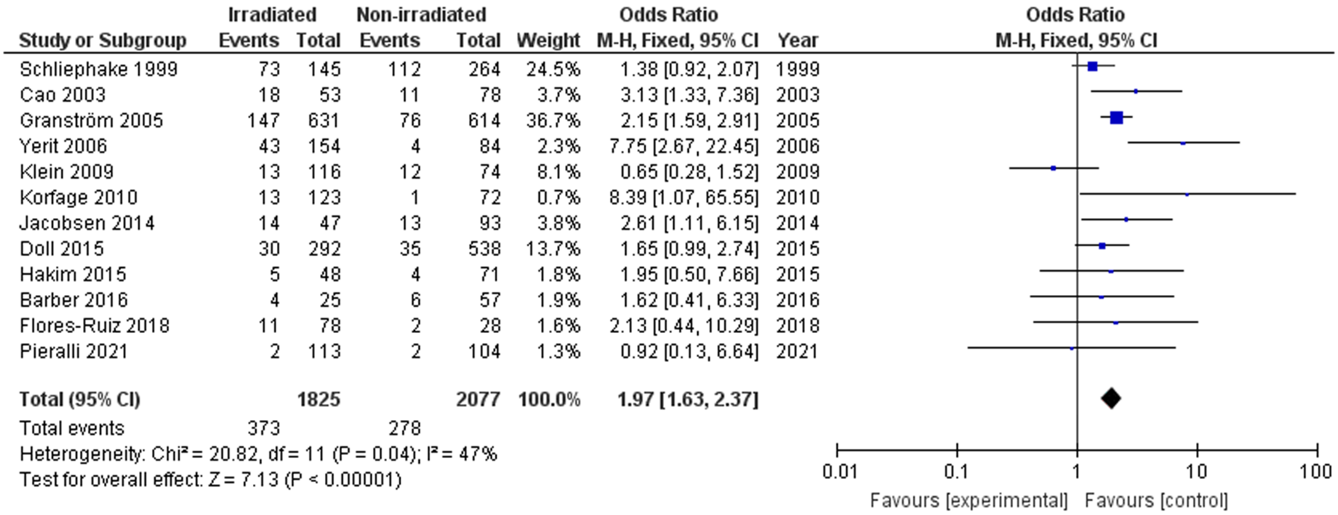


FIGURE 4 Forest plot of implant failure in irradiated versus non-irradiated bone (control) for studies with a follow-up ≥60 months (literature 1990–2021)

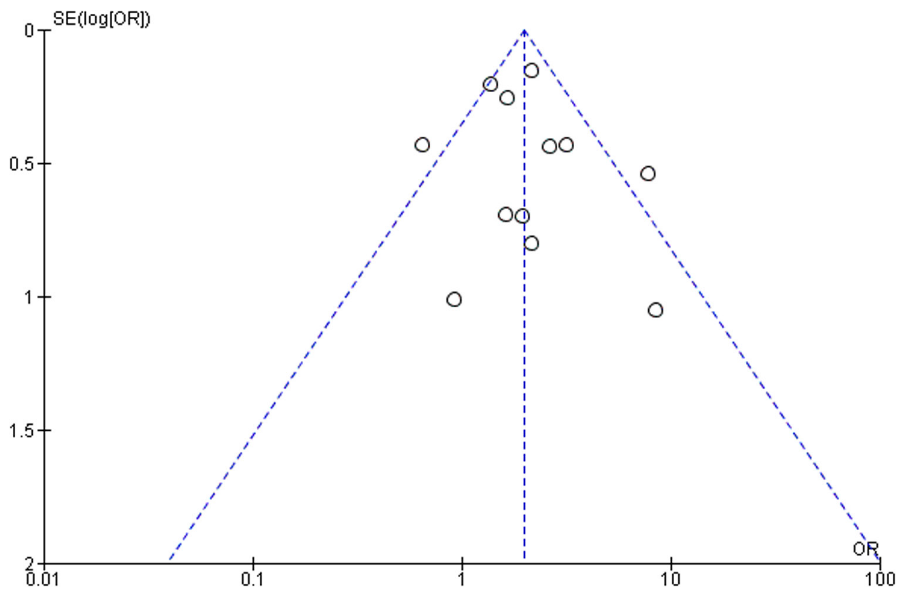


FIGURE 5 Funnel plot of analysis shown in Figure 4

the majority of studies, implant placement was performed after completion of radiotherapy. This was countered by only three studies in which the implants were inserted prior to irradiation (Alberga et al., 2020; Korfage et al., 2014; Sandoval et al., 2020). Furthermore, three studies reported implant placement both before and after radiotherapy (Ch'ng et al., 2016; Laverty et al., 2019; Moore et al., 2019). For four studies, information about the time of implantation was missing (Buurman et al., 2013; Fierz et al., 2013; Patel et al., 2020; Woods et al., 2019). With regard to radiotherapy, the studies reported high radiation doses of over 50 Gray up to 81.6 Gray (Fierz et al., 2013). Only a few studies mentioned lower values. In the partly matching studies by Pompa et al. (2015) and Di Carlo et al. (2019), radiotherapy was conducted using doses of less than 50 Gray. Moreover, some of the patients included in the studies of Hessling et al. (2015) and Rana et al. (2016) received irradiation with lower doses. In the study by Dholam et al. (2013), residual bone was irradiated with doses of 20–60 Gray, whereas bone grafts received 50–60 Gray. As only three studies reported the exact dose of radiation at the implant site Neckel et al. (2020), Alberga et al. (2020), and Papi et al. (2019) and the modality of radiotherapy differed across all studies, no further investigations on the influence of the implant-bed-specific radiation dose could be carried out.

Regarding the position of dental implants in the maxilla or mandible, the results of some studies indicated a higher failure rate for implants placed in the upper jaw (Flores-Ruiz et al., 2018; Nack et al., 2015). In total, 10 of the 29 included studies provided information about the outcome of implants depending on their position in the upper or lower jaw. Despite the inconsistency of study design and follow-up, a systematic analysis was performed including those ten studies to evaluate

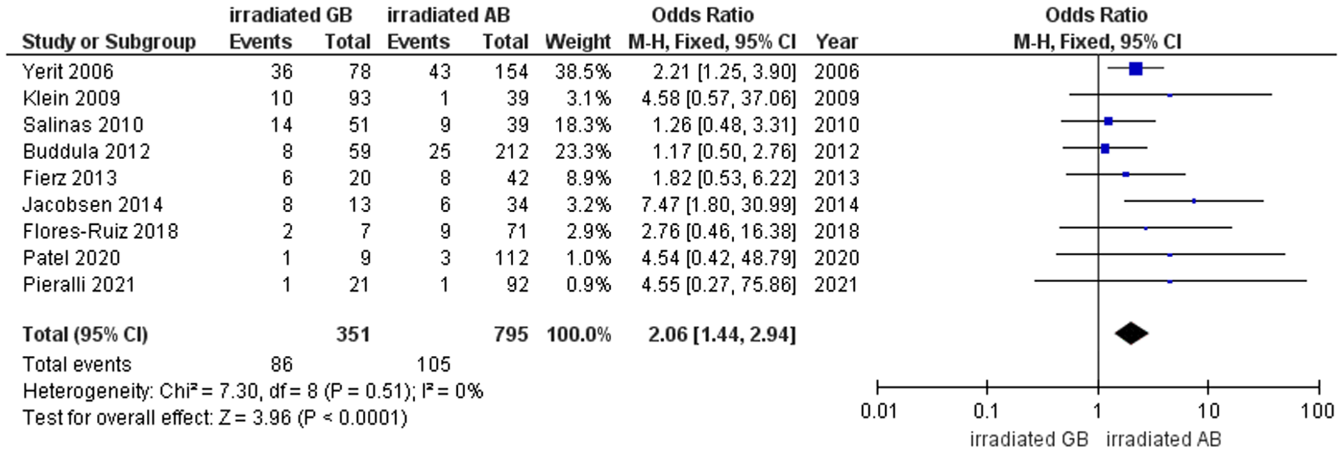
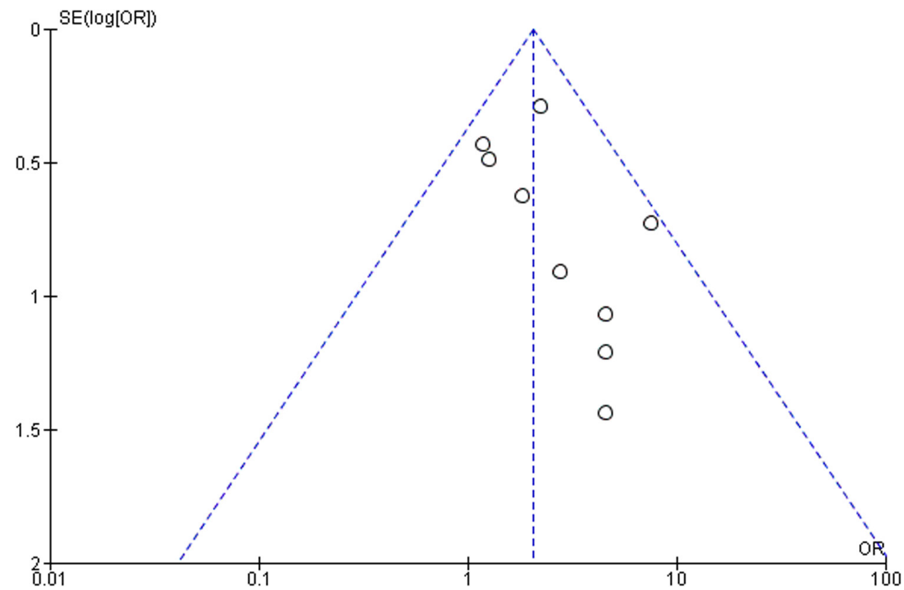


FIGURE 6 Forest plot of implant failure in irradiated grafted bone (GB) versus irradiated local bone (AB), follow-up ≥36 months (literature 1990–2021)

FIGURE 7 Funnel plot of analysis shown in Figure 6



whether an overall effect on implant survival can be observed. Data on other influencing factors such as age, gender or implant brand were too sparse and inconsistent to be used for further evaluations.

3.4 | Meta-analysis of implant survival in the irradiated jaw versus implant survival in the non-irradiated jaw

Overall, implant survival was high for studies from 2013 to 2021 with a mean rate of 91.2%. Considering all studies published between 1990 and 2021, the mean overall implant survival was 87.8% (34%–100%). Meta-analysis showed a significant influence of radiotherapy on the implant survival. Implants placed in irradiated bone were more likely to fail for studies with a follow-up ≥ three years (2013–2021, $p < .00001$, OR 2.07, CI [1.54, 2.97]) and for studies with a follow-up ≥ five years (2013–2021, $p = .003$ OR 1.8, CI [1.21, 2.67]). In the same manner when including the values examined by Schiegnitz et al. (2014), radiotherapy proves to significantly increase the risk of implant loss (1990–2021, follow-up ≥ three years $p < .00001$, OR 2.06, CI [1.75, 2.42]; follow-up ≥ five years $p < .00001$, OR 1.97, CI [1.63, 2.37]) as shown in the Figures 2–5.

3.5 | Meta-analysis of the influence of bone origin and irradiation on implant survival

Meta-analysis of the implant survival between the irradiated native bone and the irradiated grafted bone indicated a statistically significant higher implant failure in the irradiated grafted bone than in the irradiated native bone (2013–2021 follow-up ≥3 years: $p = .001$, OR 3.34, CI [1.60, 7.0], ≥5 years: $p = .001$, OR 5.14, CI [1.89, 14.02]). This result was also confirmed in the extended meta-analysis with the data from 1990 to 2021 as shown in the Figures 6–9 (*follow-up ≥ three years: $p < .0001$, OR 2.06, CI [1.44, 2.94]; follow-up ≥ five years: $p < .0001$, OR 2.26, CI [1.50, 3.40]*).

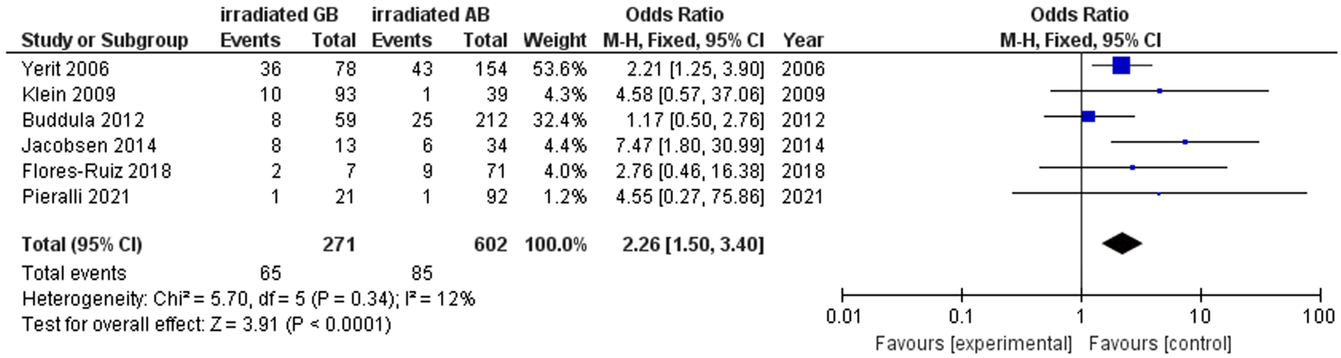


FIGURE 8 Forest plot of implant failure in irradiated grafted bone (GB) versus irradiated local bone (AB), follow-up ≥60 months (literature 1990–2021)

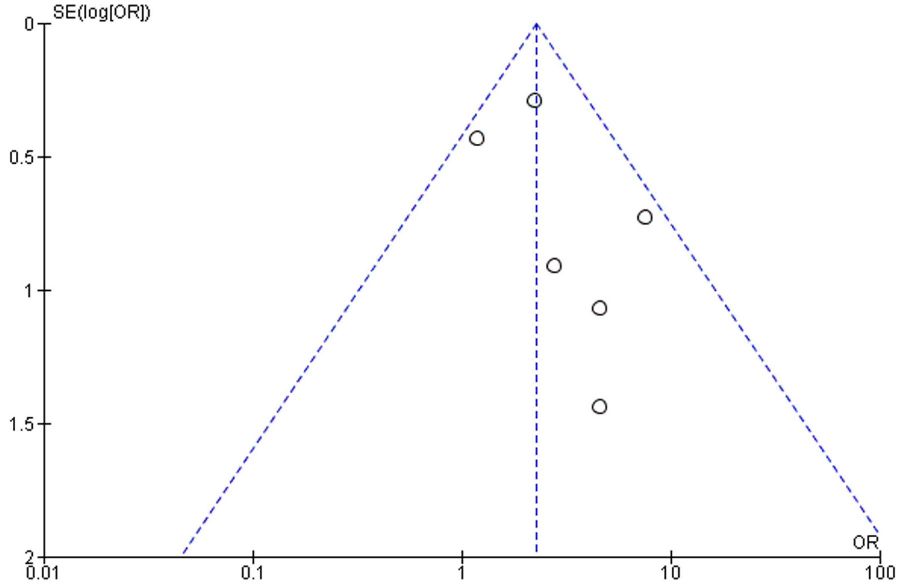


FIGURE 9 Funnel plot of analysis shown in figure

3.6 | Influence of bone origin on implant survival

When considering those studies included in this research, the following implant survival rates comparing implants placed in bone of different quality were evaluated:

- irradiated local bone: mean 89.3% (range 67.9%–98.9%)
- non-irradiated local bone: mean 95.8% (range 85.7%–100%)
- irradiated grafted bone: mean 81.4% (range 38.5%–95.2%)
- non-irradiated grafted bone: mean 91.8% (range 75%–100%)

4 | DISCUSSION

The importance of the oral rehabilitation of patients treated for head and neck cancer is beyond question, especially in view of the improvement of health-related quality of life (AWMF, 2015; Petrovic et al., 2019; Pieralli et al., 2021; Woods et al., 2019). Implant therapy plays an important role in the reconstruction of esthetical and functional defects and in the restoring of the masticatory function, particularly through better retention of the prosthetic superstructure (Buurman et al., 2013). The purpose of this review is to evaluate the outcome of dental implants placed in oral cancer patients. Even though overall implant survival is high for dental implants placed in irradiated and non-irradiated jaw, radiotherapy did prove to be a significant risk factor for implant loss in this meta-analytic approach.

In the course of the recently conducted research of studies published between 2013 and 2021, four studies showed a statistically significant correlation between a higher rate of implant failure and radiotherapy. Hessling et al. (2015) found adjuvant radiochemotherapy to significantly increase implant loss ($p = .024$). This was matched by the results of Doll et al. (2015) showing a 1.9-fold higher risk of implant loss for irradiated patients ($p = .011$). Korfage et al. (2014) also supported the finding that implants placed in irradiated patients were more likely to fail. Furthermore, Ettl et al. (2020) concluded that radiation with a dose of over 60 Gray negatively influenced implant success ($p = .025$). Contrary to that, other studies found only a minor influence of radiotherapy on the outcome of dental implantation (Alberga et al., 2020; Dholam et al., 2013; Laverty et al., 2019; Moore et al., 2019; Patel et al., 2020; Woods et al., 2019) or even resulted in comparable survival rates for implants placed in the two above-mentioned groups (Ch'ng et al., 2016; Gander et al., 2014;

Pieralli et al., 2021). All irradiated patients included into the studies by Doll et al. (2015) and Hessling et al. (2015) were treated with radiochemotherapy. This might be a reason for the higher failure rates in irradiated bone, as the combination of radio- and chemotherapy may increase the adverse effects of irradiation (Pieralli et al., 2021). Laverty et al. (2019) observed slightly, but not significantly, lower implant survival for patients treated with chemoradiation. As a matter of fact, when excluding the results found by Doll et al. (2015) from the meta-analysis of studies with a follow-up of at least 60 months, the negative influence of radiotherapy on implant survival no longer reached statistical significance. However, this observation could as well be a coincidental effect. Chemotherapy leads to bone marrow suppression resulting in leukopenia, thrombocytopenia and anaemia (Petrovic et al., 2019). Further adverse effects are for instance mucositis, pain, infection, xerostomia and neurologic problems (Wong, 2014). Nevertheless, within this research, no significant influence of chemotherapy on the outcome could be found (Ch'ng et al., 2016; Moore et al., 2019), but due to small number of cases, no conclusion can be drawn from those findings.

Regarding the type of bone, acceptable implant survival rates were observed even in bony grafts, with a mean of 89.7% ranging from 73.3% (Flores-Ruiz et al., 2018) to 100% (Woods et al., 2019), (Ernst et al., 2016). It has to be said that Woods et al. (2019) and Ernst et al. (2016) only included a small number of implants in such grafts. Hence the high implant survival of 100% found in those studies may be less meaningful. Two studies even concluded that the results for implants in grafted bone were significantly worse compared with the implant survival rates in locale bone (Ettl et al., 2020; Laverty et al., 2019). The findings of this review show that radiation of the bone graft negatively effects the outcome, as the combination of radiotherapy with implant insertion into grafted bone leads to higher failure rates (Ch'ng et al., 2016; Fierz et al., 2013; Hessling et al., 2015; Jacobsen et al., 2014). The mean overall implant survival rate in irradiated bony transplants was 81.4%. Jacobsen et al. (2014) reported a very low survival rate of 38.5% in irradiated transplanted bone, but it has to be mentioned that only a small number of 13 implants were evaluated in this subgroup. Contrary to those findings, there were also studies that described comparable implant survival in irradiated and non-irradiated grafted bone (Hakim et al., 2015; Moore et al., 2019; Sandoval et al., 2020; Woods et al., 2019) or in which the difference did not reach statistical significance (Flores-Ruiz et al., 2018; Gander et al., 2014; Patel et al., 2020). Moreover, some studies focussed only on implants placed in grafted bone (Barber et al., 2016; Burgess et al., 2017; Hakim et al., 2015; Pellegrino et al., 2018; Sandoval et al., 2020). Barber et al. (2016) compared two different types of fibula free flaps and came to the conclusion that the implants placed in bone-impacted fibula free flaps showed higher success than those placed in conventional fibula free flaps ($p = .022$). Hessling et al. (2015) found a significantly higher risk of implant loss in fibula flaps than in iliac crest and native bone.

Most implants were placed deferred after the completion of ablative surgery and radiotherapy. The opinions on the timing of implant placement vary. Some authors advocate immediate implant placement during resective surgery to shorten the interval of time between the resection and dental rehabilitation (Alberga et al., 2021; In't Veld et al., 2021;Moore et al., 2019; Woods et al., 2019). In addition, in case of adjuvant radiotherapy, immediate implant placement prior to the radiation can be beneficial as the implant healing and osseointegration takes place in non-irradiated bone (In't Veld et al., 2021; Panchal et al., 2020; Schepers et al., 2006). This may lead to higher implant survival rates (In't Veld et al., 2021). On the contrary, there are also advantages of delayed implant placement—namely the prevention of implant loss due to early recurrence of the malignancy and the possibility of proper planning of the implant placement. The latter prevents insertion of implants that cannot be used for prosthetic rehabilitation, for instance due to malposition (Alberga et al., 2020; In't Veld et al., 2021). A study by Wetzels et al. from 2017 also looked at the financial aspect of immediate and delayed implant placement and concluded that the individual costs were lower if implants were placed directly during ablative surgery, whereas the overall costs of this treatment concept were higher. With regard to the time interval between irradiation and postponed implantation, the current literature recommends implant placement at least 6 months after the completion of radiotherapy as there might be a higher risk of implant failure otherwise (Doll et al., 2015; Pellegrino et al., 2018; Petrovic et al., 2019). Di Carlo et al. (2019) stated that implants placed at least 14 months after radiotherapy were less likely to fail. Whether an implant was loaded or not and the time interval before loading were also found to be influencing the outcome. Adverse to that Moore et al. (2019), Woods et al. (2019), Jacobsen et al. (2014) and Curi et al. (2018) found no statistically significant difference in implant placement for the respective factor examined. In those studies, there was neither a difference in implant placement prior to or after radiotherapy (Jacobsen et al., 2014; Moore et al., 2019), nor in the time interval before placement after radiation (Curi et al., 2018). The same applies for immediate and delayed implants placement (Woods et al., 2019) and loading of the implant (Moore et al., 2019; Woods et al., 2019).

Due to inconsistent data, no well-founded evaluation on the influence of different modalities of radiotherapy such as intensity-modulated radiation therapy (IMRT) could be drawn within this research. For the same reason, no information can be given about the irradiation field and its effect on the outcome. IMRT is a radiation technique which allows dose distribution to minimize the delivery of radiation on the normal tissues to spare organs at risk such as the parotid glands (Hansen et al., 2012; Owosho et al., 2016; Petrovic et al., 2019; Vergeer et al., 2009). Curi et al. (2018) examined the outcomes of implants placed in irradiated patients comparing patients treated with conventional radiotherapy to a cohort that received intensity-modulated radiotherapy and found a significant difference in favour of IMRT ($p = .005$). However, this result does not correspond to the findings observed by other authors. Neckel et al. (2020) and Papi et al. (2019) for example could not find a significant difference in crestal bone loss comparing the mode of radiotherapy. Although Gander et al. (2014) reported six implant failures in only two patients treated with conventional radiotherapy compared with six implant

TABLE 1 Summary of studies on implant survival in the irradiated jaw (1990–2021)

Study	Study type	Level of evidence	No. of patients (mean age, age range in years)	No. of implants	Jaw region	Mean radiation dosage in Gy (range)
Neckel et al. (2020)	PS	IV	15 6 women (59.3, 48–71) 9 men (61.3 range, 51–71)	81	Max 26 Man 55 All in irradiated native bone	Implant bed Max 29.02 Man 45.95 per implant mean 40.7 Tumour bed 66.9 (range 54–78.2)
Pieralli et al. (2021)	RS	IIIb	57 (68.3 ± 10.3 years, 39–91) 37 patients with head and neck cancer (18 with RT, 19 without RT)	322 217 in tumour patients	Max 128 Man 194 HNC patients 217 GB 47 AB 170 RT 113 NRT 104	≤78.2
Ettl et al. (2020)	PS Results of previous publication Ettl et al. (2016)	IV	Follow-up 39 pat. Age: 60 (48–82) 52 pat at beginning Age: 62.9 (47–84) 11 patients died, 2 non-compliant	234 309 at beginning	Max 92 Man 142 GB 42 AB 192 RT 177 NRT 57	61.7 (40–72)
Patel et al. (2020)	RS	IIIb	115 (61, range 18–91)	376	Max 99 Man 277 GB 43 AB 333 RT 132 NRT 244 14 Zygoma Implants	61
Alberga et al. (2020)	PS	IIb	29 (63.4 ± 11.1, range 31–81)	58	Man RT 42 NRT 16	8 patients primary RT: tumour site 70 Gy Implant-site 32.9 ± 4.8 Gy 13 patients Postop RT: tumour site 62.4 ± 7.4, Implant-site 41.1 ± 21.5 Gy All IMRT

Origin of malignancy	Time of implant placement	Time of examination	Follow-up (months)	Implant survival rate
Squamous cell carcinoma (*n* = 13), EBV positive carcinoma (*n* = 1) MEC (mucoepidermoid carcinoma, *n* = 1) Anterior floor of the mouth (*n* = 8), oropharynx (*n* = 2), tongue (*n* = 2), maxilla (*n* = 2), nasopharynx (*n* = 1)	6 months postradiation	ND	36	Overall: 97.5%
HNC-group squamous cell carcinoma (*n* = 34), mucoepidermoid carcinoma (*n* = 1), ameloblastoma (*n* = 1), odontogenic keratocyst (*n* = 1)	6 months postradiation	ND	81.2 ± 50.3	Control group 100% HNC group 98.2% RT 98.2% NRT 98.1% GB 97.9% Irrad. GB 95.2% Non-irrad. GB 100% AB 98.2% Irrad AB 98.9% Non-irrad AB 97.4%
Primary carcinoma of the oral cavity, nasopharynx, oropharynx or laryngopharynx	45 months (range 12–217) postradiation	2009–2014	24	Overall 2 years 92.3% 1 year 94.4% Implant success Overall 2 years 78.6% 1 year 86.3% Max 73.9% Man 81.7% AB 81.2% GB 69.1% RT 76.7% Inside PTV 76.2% Outside PTV 77% NRT 86%
Squamous cell carcinoma (*n* = 55)	Placement after (70%) or during (30%) resection Time/radiation ND	2001–2018	46.92 (1.32–153.12)	Without Zygoma-implants Overall 97.5% AB 98.1% Irr. AB 97.3% Non-irr AB 98.6% GB 93% Irr GB 88.9% Non-irr. GB 94.1% RT 96.7% NRT 97.9%
Primary head and neck cancer (ND)	All during ablative surgery (immediate): average 5.3 weeks preradiation for patients with adj. RT, average 2.9 weeks preradiation for patients with primary RT	2014–2017	Median 18.5	Overall: 93.1% RT 90.5% NRT 100%

(Continues)

TABLE 1 (Continued)

Study	Study type	Level of evidence	No. of patients (mean age, age range in years)	No. of implants	Jaw region	Mean radiation dosage in Gy (range)
Sandoval et al. (2020)	RS	IV	10 with implants (70 range 50–74) control group: 10 patients without implants (not considered interesting)	29	All implants placed in irradiated fibula free flaps (postop RT)	Median 60 (60–70) 7 patients IMRT 3 patients VMAT
Di Carlo et al. (2019)	RS Patient data matches partly with Pompa et al. (2015)	IV	17 (51 ± 19)	84	Max 36 (ant. 13, post 23) Man 48 (ant 14, post 34) All in irradiated residual bone	<50
Woods et al. (2019)	RS	IIIb	20 (56, 17–91)	102	RT 51 NRT 51 GB 10 AB 92 Max and Man Immediate 39 Delayed 63	ND Post-operative radiotherapy
Laverty et al. (2019)	RS	IIIb	167 (63.2, 27–88)	779	Max 373 Man 406 GB 112 AB 650 AB+ALT and radial flap 667 RT 382 RCT: 143 RT/RCT 525 NRT 254 Placement primary 26 Delayed 753	50–70 Gy (dose not known for 30 patients)
Moore et al. (2019)	RS	IV	54 Pat (61.6) 28 Pat with oral defects 1 pat. With complex oral, nasal and orbital defect	78 dental implants Overall 160 implants	Dental implants 78 GB 38 AB 40 RT 63 NRT 15	62.7 (30–70; for all patients)
Papi et al. (2019)	PS	IV	32 (53 ± 29.7, 32–74)	113	Max 35 Man 78 Irradiated residual bone	Mean 64 ± 2.84 (range 60–70) Dose at implant site: IMRT 41 ± 1.32 3D-CRT 43 ± 1.87

Origin of malignancy	Time of implant placement	Time of examination	Follow-up (months)	Implant survival rate
Squamous cell carcinoma ($n = 7$), spindle cell ($n = 1$), osteosarcoma ($n = 1$), adenoid cystic carcinoma ($n = 1$)	2 (1–4) months preradiation (immediate implants) Median 59 days from surgery to start of RT	2015–2018	From surgery 7 (3–14) From RT completion 3.5 (0–11)	93.1%
Squamous cell carcinoma ($n = 8$), ameloblastoma ($n = 3$), osteosarcoma ($n = 2$), pleomorphic adenoma ($n = 2$), fibrous dysplasia ($n = 1$), nasopharyngeal angiofibroma ($n = 1$)	>12 months postradiation (12, 14 or 16 months) Time from surgery to implantation mean 39.58 (11–89) months	2014–2016	After implantation 22.9 (SD 15.5) After RT 39.5 SD 22.8	Overall: 90.5% Max 94.4% Ant 92.3% Post 95.7% Man 87.5% Ant 100% Post 82.4%
Malignant (70%) or benignant (30%) diseases Implants: Malignant 68 Benignant 34	ND	11-year period (all patients treated after 2017, except for 2 patients treated in 2002)	23 (range 2–140)	Overall 93.1% RT 90.2% NRT 96.1% GB 100% AB 92.4%
Squamous cell carcinoma ($n = 128$), adenoid cystic carcinoma ($n = 7$), ameloblastoma ($n = 7$), malignant melanoma ($n = 3$), osteogenic sarcoma ($n = 3$), mucoepidermoid ($n = 2$), pleomorphic adenoma ($n = 2$), BCC ($n = 2$), adenocarcinoma ($n = 2$), primitive neuroectodermal tumour ($n = 1$), chondrosarcoma ($n = 1$), odontogenic keratocyst ($n = 1$), lymphoma ($n = 1$), dendritic cell sarcoma ($n = 1$), pindborg-tumour ($n = 1$), unspecified carcinoma/tumour ($n = 1$)	Preradiation ($n = 27$) and postradiation ($n = 498$)	2012–2017	Mean 43 (range 1–142) Median 38	Overall: 95.6% RT/RCT 95% RT 96.1% RCT 92.3% NRT 96.9% AB 98.2% AB+ALT and radial flap 97.8% GB 83% scapula 100% fibula 83.1% DCIA 76.0% Iliac crest (non-vascular) 80.0%
Squamous cell carcinoma ($n = 39$), adenoid cystic carcinoma ($n = 6$), melanoma ($n = 2$), ORN ($n = 2$), basal cell carcinoma ($n = 1$), mucoepidermoid carcinoma ($n = 1$), nerve-sheath carcinoma ($n = 1$), neuroendocrine carcinoma ($n = 1$), sebaceous carcinoma ($n = 1$)	30 patients at time of resection, 20 delayed after RT, 4 patients both 74 implants preradiation 64 implants postradiation (all patients)	2010–2018	25.7 (6–89) Pat with RT mean 27, NRT mean 18.3 months (all patients)	Dental implants Overall 85.9% AB 87.5% GB 84.2% RT 82.5% NRT 100%
Squamous cell carcinoma ($n = 19$), ameloblastoma ($n = 6$), osteosarcoma of the jaw ($n = 3$), carcinoma ex pleomorphic adenoma ($n = 4$)	>12 months (12–24) postradiation	2014–2015	25,5 ± 3.4 (range 24–30) months after prosthetic rehablilitation	Overall: 94.7% Max 91.4% Man 96.2%

(Continues)

TABLE 1 (Continued)

Study	Study type	Level of evidence	No. of patients (mean age, age range in years)	No. of implants	Jaw region	Mean radiation dosage in Gy (range)
Curi et al. (2018)	RS	IV	35 (65, 46–94)	169	Max 79 Man 90 All in irradiated bone	mean 62 (50–70) Conventional RT (24 patients) IMRT (11 patients)
Flores-Ruiz et al. (2018)	RS	IIIb	17 Age 30–39 ($n = 2$) 40–49 ($n = 2$) 50–60 ($n = 5$) >60 ($n = 8$)	106	Max 43 Man 63 GB 15 (Max 7, Man 8) AB 91 (36 Max, Man 55) RT 78 NRT 28	ND
Burgess et al. (2017)	RS	IIIb	59 (51 range 18–77)	199 All in GB	FF 96 DCIA 64 Scapula 37 Radius 2 RT 45 NRT 154	>60–66
Rana et al. (2016)	RS	IV	46 (60 ± 25)	162	Max 70 ant 35, post 35 Man 92 ant 52, post 40 Irradiated bone	<50 ($n = 19$ patients, 31 implants) 51–70 ($n = 16$ patients, 61 implants) >71 ($n = 11$ patients, 70 implants)
Ernst et al. (2016)	RS	IIIb	36 (65.8, 39–90)	194	Max 73 Man 121 GB 12 AB 182 RT 88 NRT 106	55–72 IMRT
Barber et al. (2016)	RS	IIIb	114 (54) 30 patients with implants	82 All in GB	FFF 35 (RT 12; NRT 23) BIFFF 47 (RT 13; NRT 34) RT 25 NRT 57	ND

Origin of malignancy	Time of implant placement	Time of examination	Follow-up (months)	Implant survival rate
Squamous cell carcinoma tongue (*n* = 8), floor of the mouth (*n* = 6), maxillary alveolus (*n* = 6), gingiva (*n* = 5), buccal mucosa (*n* = 4), oropharynx (*n* = 3), retromolar area (*n* = 2), palate (*n* = 1)	mean 23.7 (1–92 months) postradiation	1995–2010	89.16 (Range: 3.6–176.4)	Overall: 92.9% Max 91.1% Man 94.4% 5y success rate Max 92.4% Man 90.9% (*p* = .808)
Squamous cell carcinoma (*n* = 15) osteosarcoma (*n* = 1) lymphoepithelioma (*n* = 1)	Postradiation/Delayed implant placement (after cancer treatment)	1991–2011	60	Overall 87.7% Max 79.1% Man 93.7% GB 73.3% Irrad. GB 71.4% Non-irrad. GB 75% AB 90.1% Irrad.AB 87.3% Non-irrad. AB 100% RT/RCT 85.9% NRT 92.9%
Head and neck neoplasm: mandibular alveolus (*n* = 25), maxilla (*n* = 24), tongue/floor of mouth (*n* = 6) and others (oropharynx, buccal mucosa)	Mean 15 (4–41) months postradiation 19 (0–141) after reconstruction	2009–2015	24 (6–60) from surgery	Overall 94.5% RT 84.4% NRT 97.4% FF 91.7% DCIA 96.9% Scapula 97.3% Radius 100%
Oral cancer (ND)	Mean 15 (6–24) Postradiation implants placed post RT 6–12 months *n* = 49 12–18 months *n* = 54 18–24 months *n* = 59	2002–2008 (2003–2009)	60	Overall: 67.9% Max 71.4% Ant 65.7% Post 77.1% Man 65.2% Ant 65.4% Post 65%
Squamous cell carcinoma	>6 months postradiation	ND	52.92 (24–117)	Overall 97.9% Max: 100% Man: 96.7% GB (non-irradiated) 100% AB 97.8% Irrad. AB 96.6% Non-irrad. AB 98.9% RT: 96.6% NRT: 99.1%
Head and neck cancer (ND) T1 (*n* = 6) T2 (*n* = 14) T3 (*n* = 24) T4 (*n* = 72) Overall 116 cases in 114 patients	Postradiation	2001–2009	60	Overall 87.8% RT 84% NRT 89.5% FFF 77.1% RT FFF 83.3% NRT FFF 73.9% BIFFF 95.7% RT BIFFF 84.6% NRT BIFFF 100% >10 packyears smokers 93.1%

(Continues)

TABLE 1 (Continued)

Study	Study type	Level of evidence	No. of patients (mean age, age range in years)	No. of implants	Jaw region	Mean radiation dosage in Gy (range)
Ch'ng et al. (2016)	RS	IIIb	246 (59)	1132	AB 889 Max 271 Man 618 GB (FFF) 243 RT 795 preop 100 postop 695 NRT 337	60–72 IMRT
Pompa et al. (2015)	RS Patient data matches partly with Di Carlo et al. (2019)	IIIb	34 (51 ± 19)	168	Max 72 (26 ant, 46 post) Man 96 (28 ant, 68 post) RT 51 NRT 117	<50
Hessling et al. (2015)	RS	IIIb	59 (55, 18–77)	272	Max 83 Man 189 AB 179 GB 93 RCT 223 neoadj. 95 adj. 128 NRT 49	Neoadjuvant 40 Gy (21 patients) Adjuvant 61–66 Gy (28 patients)
Nack et al. (2015) *5-year follow-up of a previous publication* (Heberer et al. 2011)	RS	IV	20 (61.1)	97 (48 SLA, 49 SLActive) (102 at beginning, 50 SLA, 52 SLActive)	Max 47 Man 35 Irradiated bone (Max 55; Man 47 at beginning)	≤72 Adjuvant RCT
Doll et al. (2015) *Based partly on data published by* Nelson et al. (2007)	RS	IIIb	157 (53.7, 16–79)	830	Max 450 Man 380 RT 292 (Max 74; Man 118) NRT 538	50–72

Origin of malignancy	Time of implant placement	Time of examination	Follow-up (months)	Implant survival rate
Squamous cell carcinoma ($n = 182$), adenoid cystic carcinoma ($n = 10$), osteosarcoma ($n = 7$), ameloblastic carcinoma ($n = 6$), desmoid tumour ($n = 4$), fibrosarcoma ($n = 3$), adenocarcinoma ($n = 3$), melanoma ($n = 3$), mucoepidermoid carcinoma ($n = 3$), haemangioendothelioma ($n = 1$), ORN ($n = 25$)	147 patients preradiation (695 implants) 18 patients postradiation (100 implants) 41 of those patients with definite RT (implants placed 4–6 weeks preradiation)	2005–2011	Median 33.7 (0.9–92.7)	Overall 96.3% (3 years 92.8%, 5 years 92.2%) Max 97.8% Man 97.4% GB (FFF) 91.8% Irrad. GB 83.3% Non-irrad. GB 94.9% AB 97.5% Irrad. AB 97.4% Non-irrad. AB 98.1% RT 96.2% preop RT 92% postop RT 96.8% NRT 96.4%
Squamous cell carcinoma ($n = 16$), ameloblastoma ($n = 6$), osteosarcoma ($n = 4$), pleomorphic adenoma ($n = 4$), fibrous dysplasia ($n = 2$), nasopharyngeal angiofibroma ($n = 2$)	39.58 (12–89) months after surgery and radiation therapy	2007–2012	After RT 39.5 SD 22.8 After Implant placement 22.9 SD 15.5	Overall 90.5% Max 94.4% Man 87.5% RCT 76.5% NRT 96.6% Max ant 92.3%, post 95.7% Man ant 100%, post 82.4%
Squamous cell carcinoma ($n = 53$), odontogenic tumour with malignant degradation ($n = 4$) sarcoma ($n = 2$),	Postradiation “after ablative surgery, RT and RCT implants were placed during the reservation time”	2003–2011	30.9 (3–82)	Overall 2 years 98.9%, 5 years 97.1% During observation time (≤82 months) 96.3% After 5 years GB 94,6% AB 98.3% RCT 96.4% Neoadj. 97.9% Adj. 95.3% NRT 100%
Malignant tumour of the mandible (ND)	>6 months postradiation	ND	60 (36–72)	Overall (after 5 years) 79.4% SLA 79.2% SLActive 79.6%
malignant tumour of oral cavity floor of the mouth ($n = 150$) maxillary area ($n = 7$)	>6 months postradiation	ND	121 (37–240)	Overall 92.2% Max 92% Man 92.4% NRT 93.5% RT 89.7%

(Continues)

TABLE 1 (Continued)

Study	Study type	Level of evidence	No. of patients (mean age, age range in years)	No. of implants	Jaw region	Mean radiation dosage in Gy (range)
Hakim et al. (2015)	RS	IIIb	37 (51.8 ± 10.6)	119	Max and Man all in GB (fibula free flaps) RT 48 NRT 71	ND
Jacobsen et al. (2014)	RS	IV	33 (52.4, 20–69) 23 patients with implants	140	Man RT 47 NRT 93 GB 99 irrad. GB 13 non-irrad. GB 86 AB 41 irrad. AB 34 non-irrad. AB 7	63 (50–73)
Korfage et al. (2014)	PS	IIIb	164 (64.8, 39–88)	524	Native Man RT 318 NRT 206	ND
Gander et al. (2014)	RS	IIIb	33 (64.15 ± 7.6)	136	All in Man GB 48 AB 88 RT 84 NRT 52	56–76
Dholam et al. (2013)	RS	IV	30 (46, 13–82)	85	GB 40 AB 45 RT 59 NRT 26 Max and Man	20–60 AB 20–60 GB 50–60
Buurman et al. (2013)	RS	IV	51 (67.2, 52–84) 32 patients with implants	73	Irradiated Man	ND

Origin of malignancy	Time of implant placement	Time of examination	Follow-up (months)	Implant survival rate
Oral cancer (*n* = 23, including 1 patient with ORN), benign bone lesion, odontogenic tumour (*n* = 8) Fracture (*n* = 1) High-grade atrophy (*n* = 2)	postradiation NRT 6 months after reconstruction RT 12 months after RT (recurrence free; Information given in Figure 8)	1993–2012	94.5 ± 37.3 (3–172)	Overall 92.4% RT 89.6% NRT 94.4% 9 implants had to be explanted (bone resorption/local osteomyelitis) 1 implant "sleeping" (malpositioning)
Squamous cell carcinoma (*n* = 10), osteosarcoma (*n* = 1), malignant peripheral neural tumour (*n* = 1), osteoradionecrosis (*n* = 14), ameloblastoma (*n* = 1), osteomyelitis (*n* = 2), facial trauma (*n* = 2), mandibular atrophy (*n* = 2)	17 months (4–48) after reconstruction Radiotherapy within 6 months after reconstruction Tumour patients after 1 year without recurrence	1997–2005	Median 67	Overall 80.7% 1 year 93.6% 5 years 83.3% RT 70.2% NRT 86% GB 79.8% Irr GB 38.5% Non-irr GB 86% AB 85.4% Irr AB 82.4% Non-irr AB 85.7%
Squamous cell carcinoma (of the tongue, floor of the mouth, mandibular gingiva, buccal mucosa, lower lip, or tonsil)	Immediately after resection 6 weeks preradiation	1998–2010	45.6 (0–174)	Overall 93,1% RT 90,3% NRT 97,6%
Squamous cell carcinoma (*n* = 29), ameloblastoma (*n* = 1), adenocarcinoma (*n* = 1), ORN (*n* = 1), BONJ (*n* = 1)	42.1 (12–165) months postradiation	2006–2012	20	Survival = osseointegration of implant, absence of pain, intact overdenture = success Overall after 20 months 87.5% after 12 months 92.7% GB 87.5% AB 87.5% RT 85.7% NRT 90.4%
Squamous cell carcinoma (*n* = 15), verrucous cell carcinoma (*n* = 3), ameloblastoma (*n* = 2), verrucous hyperplasia, epidermoid carcinoma, mucoepidermoid carcinoma, melanoma, fibroma, Langerhans-cell-histiocytosis, chondroblastic osteogenic sarcoma, aneurysmal bone cyst, primary neuroectodermal tumour, undifferentiated carcinoma (each *n* = 1)	12 months postradiation	2003–2008	60	Survival rate ND Rate of osseointegration (ROI) Overall 88% GB 93% AB 85% RT 83% NRT 100% Success rate Overall 76.5% GB 72.5% AB 80% RT 71.2% NRT 88.5%
Head and neck cancer Most frequent locations: oral (*n* = 23), oropharynx (*n* = 14), laryngopharynx (*n* = 11) Other (*n* = 3)	ND	2006–2011	Overall follow-up 69 (12–276) implant-follow-up 48.6 (14–132)	97.3% Success rate 95.9%

(Continues)

TABLE 1 (Continued)

Study	Study type	Level of evidence	No. of patients (mean age, age range in years)	No. of implants	Jaw region	Mean radiation dosage in Gy (range)
Fierz et al. (2013)	RS	IV	46 (57 ± 7.2) 28 patients with implants	104	Max 28 Man 76 GB 46 AB 58 RT 62 NRT 42	56–81.6
Buddula et al. (2012)	RS	IV	48 (60.2, ND)	271	Max, Man	60.7 (50.2–75.5)
Mancha de la Plata et al. (2012)	RS	IIIb	30 (55.5, 40–74) RT 10 NRT 20	355	Max, Man RT 225 NRT 130	59.6 (50–70)
Linsen et al. (2012)	RS	IIIb	66 (55.7, 6–82)	262	Max, Man RT 127 NRT 135	36 or 60
Fenlon et al. (2012)	CSS	IV	41 (ND)	145	Max, Man RT 35 NRT 110	ND
Buddula et al. (2011)	RS	IV	48 (60.2, ND)	271	Max, Man GB 118 AB 212	60.7 (50.2–75.5)
Bodard et al. (2011)	RS	IV	23 (46, 17–66)	75	GB Man	ND
Sammartino et al. (2011)	PS	IV	77 (55.8, 26–63)	188	Max, Man	<50 or >50

Origin of malignancy	Time of implant placement	Time of examination	Follow-up (months)	Implant survival rate
Squamous cell carcinoma (n = 35), adenocarcinoma (n = 4), non-Hodgkin-lymphoma (n = 1), angiosarcoma (n = 1), multifocal plasmacytoma (n = 1), verrucous carcinoma (n = 1), esthesioneuroblastoma (n = 1), uncertain/metastases (n = 2)	ND	2004–2007	36–72	Overall 82.7% GB 82.6% Irr GB 70% Non-irr. GB 92.3% AB 82.8% Irrad. AB 81% Non-irrad. AB 87.5% RT 77.4% NRT 90.5%
Squamous cell carcinoma, adenoid cystic carcinoma, basal cell carcinoma, unknown primary head and neck carcinoma	41 months postradiation	1987–2008	60	Overall 89.9% Max 80.5% Man 93.6% AB 93.4% GB 83.3%
Squamous cell carcinoma, adenoid cystic carcinoma, basal cell carcinoma	33 months postradiation (12–96)	2000–2007	60	RT 92.6% NRT 96.5% Osteoradionecrosis 48.3% Non-osteoradionecrosis 92.3%
Squamous cell carcinoma, ameloblastoma, adenoid cystic carcinoma, keratocysts	41 months postradiation (6–126)	1997–2008	42	Overall 86.9% (10-year) RT 95.6% (10-year) RT and chemotherapy 91.5% (5-year) NRT 84.7% (10-year)
ND	ND	ND	Time of surgical reconstruction or after 3 months of healing	Irrad. GB 57% Non-irrad. GB 97% Immediate placement 35% Non-immediate 96%
Squamous cell carcinoma, adenoid cystic carcinoma, basal cell carcinoma, unknown primary head and neck carcinoma	41 months postradiation	1987–2008	23 (5–203) AB/GB 36	Turned implants Max 72.6% (5 years) Turned implants Man 91.7% (5 years) Roughened implants Max 87.5% (5 years) Roughened implants Man 100% (5 years) GB, Max 82.3% GB, Man 98.1%, AB; Max 79.8% AB, Man 100%
ND	ND	ND	27.5 (1–71)	Irrad. GB 80%
ND	>6 months postradiation	2004–2006	36	Overall 89.4% RT Max 57.1% RT Man 98.4% >50 Gy 78.6% < 50 Gy 93.6%

(Continues)

TABLE 1 (Continued)

Study	Study type	Level of evidence	No. of patients (mean age, age range in years)	No. of implants	Jaw region	Mean radiation dosage in Gy (range)
Heberer et al. (2011) Preliminary results, final results reported by Nack et al. (2015)	PS	IV	20 (61.1, 45–79)	102 SLA: 50 modSLA (=SLActive) 52	Max, Man	<72
Salinas et al. (2011)	RS	IV	44 (ND)	206	Man RT 90 NRT 116	>60
Korfage et al. (2010)	PS	IIb	50 (61.5, 41–81)	195	Max, Man RT 123 NRT 72	>40 (12–70)
Klein et al. (2009)	RS	IIIb	68	190	Max, Man RT > 50 Gy 61 NRT 75	<50 or > 50
Cuesta-Gil et al. (2009)	RS	IV	111 (52, 13–79)	706	ND	ND (50–60)
Schoen et al. (2008)	PS	IIb	50 (61.5, 41–81) RT: 31 NRT: 19	186	Max, Man RT 124 NRT 62	60.1
Nelson et al. (2007)	RS	IV	93 (59, 26–89) RT: 29	435	Max, Man RT 124	<72
Schoen et al. (2007)	PS	IV	26 (60.1, 47–77)	103	Man	61.4 (46–116)
Yerit et al. (2006)	RS	IIIb	71 (57.8, 16–84.1)	316	Man Irrad. AB 154 Irrad GB 78 NRT (AB) 84	50 (ND)
Schepers et al. (2006)	RS	IIIb	48 (64,8, 54–75) RT: 21 C: 27	139	Man RT 61 NRT 78	ND (60–68)
Granström (2005)	RS	IIIb	207 (59.1, 12–90) RT: 107 NRT: 100	1245	Max, Man RT 631 NRT 614	ND
Cao et al. (2003)	RS	IIIb	27 (45–79)	131	Max, Man RT 53 NRT 78	ND (36–76)

Origin of malignancy	Time of implant placement	Time of examination	Follow-up (months)	Implant survival rate
ND	>6 months postradiation (9.4)	ND	14.4 (12–26)	SLA 96% modSLA (SLActive) 100%
Squamous cell carcinoma, tonsillar carcinoma, adenoid cystic carcinoma, rhabdomyosarcoma, osteosarcoma, unknown primary head and neck carcinoma	ND	1994–2006	41.1 (4–108)	Overall 85% RT 74.4% NRT 93.1% Irrad GB 72.5% Non-irrad. GB 90.4% Irrad. AB 76.9% Non-irrad. AB 96.2%
Squamous cell carcinoma	Preradiation	1998–2002	60	RT (AB) 89.4% NRT (AB) 98.6%
Squamous cell carcinoma	Postradiation	1992–2004	60	Overall 86.8% RT 88.8% RT ≥50 Gy 85.2% % RT <50 Gy 92.7% NRT 83.8% Irrad GB 89.2% Non-irrad GB 68.6% Irrad AB 97.4% Non-irrad AB 91.3%
Malignancies and ameloblastomas	>12 months postradiation (in 34 cases)	1995–2010	108	92.9%
Squamous cell carcinoma	6 weeks preradiation	1998–2002	18–24	RT (AB): 97% NRT (AB): 97%
ND	Postradiation	1992–2005	120 (5–161)	Overall: 70% (8 years) Overall: 69% (13 years) RT: 84% (3.8 years) RT: 54% (13.5 years)
Squamous cell carcinoma	>12 months postradiation	1990–2000	36	93.9% HBO: 85.2%
Squamous cell carcinoma	Approx. 18 months postradiation	1990–2003	60 (4–151)	Overall: 75% (8-year) Irrad AB: 72% (8 years) Irrad GB 54% (8 years) NRT (AB) 95% (8 years)
Squamous cell carcinoma	>3 months preradiation	1996–2003	>30	RT 97% NRT: 100%
Squamous cell carcinoma, adenoid cystic carcinoma, malignant ymphoma, other carcinoma	Pre- and postradiation	1979–2004	72 (6–276)	RT: 75% NRT: 87%
Squamous cell carcinoma, adenocarcinoma, fibrosarcoma, basal cell carcinoma	ND	1994–2000	60	Overall: 65% RT: 49.44% NRT: 77.8%

(Continues)

TABLE 1 (Continued)

Study	Study type	Level of evidence	No. of patients (mean age, age range in years)	No. of implants	Jaw region	Mean radiation dosage in Gy (range)
Visch et al. (2002)	PS	IV	130 (62, 34–87)	446	Max, Man	ND
Grötz et al. (1999)	RS	IV	47 (ND)	197	Max, Man	ND (36–70)
Betz et al. (1999)	PS	IV	59 (ND)	261	Max, Man	40 (ND)
Weischer and Mohr (1999)	RS	IIIb	49 (55, 43–75) RT: 18 NRT: 22	175	Man RT 83 NRT 92	50 (36–72)
Schliephake et al. (1999)	RS	IIIb	38 (51.9, 16–77) RT: 30	409	Max, Man RT 145 NRT 264	ND (32–60)
Werkmeister et al. (1999)	RS	IV	138 (55, 35–79)	109	Max, Man RT 30 NRT 79	54 (42–64)
Niimi et al. (1998)	RS	IV	44 (ND)	228	Max, Man	ND (25–66)
Keller et al. (1997)	RS	IV	19 (57, 24–84)	98	Man	56 (27–70)
Esser and Wagner (1997)	RS	IV	60 (ND)	221	Man	60 (ND)
Jisander et al. (1997)	RS	IV	17 (67, 47–78)	103	Max, Man	ND
Watzinger et al. (1996)	RS	IV	26 (ND, 41–79)	138	Man	50 (ND)

Abbreviations: AB, alveolar bone/local bone; CSS, cross sectional study; GB, grafted bone; irrad., irradiated; Man, mandible; Max, maxilla; ND, no data available or data cannot be separated; non-irrad., non-irradiated; NRT, No Radiotherapy (Control group); PS, prospective study; RS, retrospective study; RT, radiotherapy group.

failures in 19 patients treated with IMRT, there was no significant difference found between IMRT and conventional radiotherapy due to the small number of patients receiving conventional radiotherapy. In this review, many studies reported the use of dose distributing techniques such as IMRT and volume-modulated arch therapy (VMAT (Teoh et al., 2011)) as radiation modality for at least some or even all patients (Alberga et al., 2020; Ch'ng et al., 2016; Curi et al., 2018; Ernst et al., 2016; Gander et al., 2014; Neckel et al., 2020; Papi et al., 2019; Pieralli et al., 2021; Sandoval et al., 2020). In fact, the literature found on this subject strongly recommends the use of IMRT as it shows good rates of locoregional control and has positive effects on the quality of life (Anand et al., 2008; Graff et al., 2007; Nutting et al., 2011; Peponi et al., 2011; Setton et al., 2012). This can be seen from lower rates of dysphagia, xerostomia, mucositis and trismus through lower radiation exposure of the normal tissues (Gomez et al., 2011; Lohia et al., 2014; Owosho et al., 2016; Petrovic et al., 2019; Vergeer et al., 2009). Furthermore, there are studies describing a beneficial influence of IMRT on the risk of developing ORN. (Davis et al., 2021; Gomez et al., 2011; Owosho et al., 2016). Another technique approved by current literature is the proton beam radiotherapy (PBRT) that may have an even greater effect on dosage reduction in the surrounding tissues and organs (Owosho et al., 2016; Petrovic et al., 2019; Romesser et al., 2016).

As has been mentioned, osteoradionecrosis (ORN) is a feared complication. This chronic side effect of irradiation appears in 1%–37.5% of cases and can lead, inter alia, to pain, fracture of the mandible, or sequestration of devitalized bone (Petrovic et al., 2019). Radiation therapy with high doses of over 60 Gray significantly increases the risk of this complication (Davis et al., 2021; Hansen et al., 2012; Koudougou et al., 2020; Petrovic et al., 2019; Reuther et al., 2003; van Baar et al., 2021). In the context of this review, Ch'ng et al. (2016) found smoking to be a significant risk factor for the development of osteonecrosis after radiotherapy (p = .027), which is in line with the findings of the literature (Reuther et al., 2003). The development of osteoradionecrosis can be caused by lesions due to extraction of teeth or implant placement. Due to the radiation-induced

Origin of malignancy	Time of implant placement	Time of examination	Follow-up (months)	Implant survival rate
Head and neck cancer	>6 months postradiation	1987–2001	120	78%
ND	Pre- and postradiation	1988–1997	72	72%
Squamous cell carcinoma	Postradiation	1988–1996	ND	77.8%
Squamous cell carcinoma	48 months postradiation (13–189)	1988–1997	37	Overall 91% (3 years) RT 75% (7 years) NRT 86% (10 years)
ND	20 months postradiation	ND	120	RT 49.8% NRT 57.7%
Squamous cell carcinoma	>24 months postradiation	1991–1993	36	RT 73% NRT 85%
ND	ND (1–240) postradiation	ND	<24	Japan 88.9% USA 86%
Squamous cell carcinoma, basal cell carcinoma, lymphoma, histiocytosis, pleomorphic sarcoma	72 months postradiation (16–168)	1986–1994	120	99%
ND	>9 months postradiation	1985–1995	60	80%
ND	88 months postradiation (18–28)	ND	21 (1–62)	Max 92% (1 year) Man 97% (1 year)
Squamous cell carcinoma	Postradiation	1990–1996	36	AB 87.8% GB 58.3%

hypocellularity and hypovascularity, a chronic non-healing wound occurs. (Petrovic et al., 2019; Reuther et al., 2003; van Baar et al., 2021). A common treatment of ORN is the hyperbaric oxygen treatment (HBOT; Davis et al., 2021; Marx & Johnson, 1987; Reuther et al., 2003), which increases the amount of dissolved oxygen in the plasma and leads to higher blood flow and cellular activity in the tissues (Esra Nur Avukat, Canan Akay, 2020). Some of the investigated studies mentioned HBO treatment for patients receiving radiotherapy, but none of them provided evidence about the influence of this treatment on implant survival or prevention of ORN. Ch'ng et al. (2016) came to conclusion that HBOT had no effect on implant success. The currently published literature also does not provide clear recommendation for application of HBOT in head and neck cancer patients (Chrcanovic et al., 2016; In't Veld et al., 2021; Koudougou et al., 2020; Shaw et al., 2019).

As radiation may increase inflammatory cytokines, radiotherapy can trigger acute inflammation (Costa & Reagan, 2019). Furthermore, the cytotoxic effect on the oral mucosa tissue is high due to the high turnover rate and low radiation resistance of mucosal cells. The development of a radiation-induced mucositis could be the consequence. This may result in mucosal breakdown and ulceration accompanied by pain and restricted oral function (Pakravan et al., 2019; Wong, 2014). Moreover, peri-implantitis and mucositis often lead to progressive bone loss and implant failure (Doll et al., 2015; Hessling et al., 2015; Pellegrino et al., 2018; Pieralli et al., 2021). Neckel et al. (2020) and Ernst et al. (2016) both reported a significantly higher bone loss for implants placed in irradiated bone ($p<.001$). The health of the surrounding soft tissues is an important factor influencing implant success for grafted bone and for native bone. In many studies, vestibuloplasty was performed, especially for irradiated patients. Pieralli et al. (2021) concluded that the stabilization of the soft tissues benefits the long-term outcome of dental implants and can be achieved through skin grafts. To prevent inflammation, antibiotic prophylaxis was given in all studies, some even used extended antibiotic regimen for irradiated patients. Knowing about the danger of peri-implantitis in the studies conducted by

TABLE 2 Risk of bias evaluation—Newcastle-Ottawa scale

Study	Selection (max. 4 ★)				Comparability (max. 2 ★)	Outcome (max. 3 ★)			Total
	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interst was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total number of stars, quality of study
Pieralli (2021)	★	★	★	★	★	★	★	★	8, good
Ettl (2020)	0	★	★	★	0	★ *success*	★	★	6, poor (success)
Patel (2020)	★	★	★	★	★	★	★	★	7, good
Alberga (2020)	★	★	★	★	★	★	★	★	8, good
Woods (2019)	0	0	★	★	★	★	★	★	6, fair
Laverty (2019)	★	★	★	★	★	★	★	★	8, good
Moore (2019)	0	0	★	★	★	★	★	★	6, fair
Flores-Ruiz (2018)	★	★	★	★	★	★	★	★	8, good
Burgess (2017)	0	0	★	★	★	★	★	★	6, fair
Ernst (2016)	★	★	★	★	★	★	★	★	8, good
Barber (2016)	0	0	★	★	0	★	★	★	5, poor
Ch'ng (2016)	★	★	★	★	★	★	★	★	8, good
Pompa (2015) *Data matching partly with*	★	★	★	★	★	★	★	★	8, good
Doll (2015) *Based partly on Nelson* (2007)	★	★	★	★	★	★	★	★	8, good
Hakim (2015)	0	★	★	★	★	★ *success*	★	★	7, good (success)
Jacobsen (2014)	0	★	★	★	0	★	★	★	6, poor
Korfage (2014)	★	★	★	★	★	★	★	★	8, good
Gander (2014)	★	★	★	★	★	★	★	★	8, good
Dholam (2013)	★	★	★	★	★	★ *success*	★	★	8, good (success)

TABLE 2 (Continued)

Study	Selection (max. 4 ★)				Comparability (max. 2 ★)	Outcome (max. 3 ★)			Total
	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interst was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total number of stars, quality of study
Fierz (2013)	★	★	★	★	0	★	★	★	7, poor
Mancha de la Plata (2012)	★	★	★	★	★	★	★	★	8, good
Linsen (2012)	★	★	★	★	★	★	★	★	8, good
Fenlon (2012)	0	0	★	★	0	★	★	★	5, poor
Salinas (2011)	0	0	★	★	0	★	★	★	5, poor
Korfage (2010)	★	★	★	★	★	★	★	★	8, good
Klein (2009)	0	★	★	★	★	★	★	★	7, good
Schoen (2008)	★	★	★	★	★	★	★	★	8, good
Yerit (2006)	★	★	★	★	★	★	★	★	8, good
Schepers (2006)	★	★	★	★	★	★	★	★	8, good
Granström (2005)	★	★	★	★	★	★	★	★	8, good
Cao (2003)	★	★	★	★	★	★ *success*	★	★	8, good
Weischer (1999)	★	★	★	★	★	★	★	★	8, good
Schliephake (1999)	★	★	★	★	★	★	★	★	8, good
Werkmeister (1999)	★	★	★	★	0	★	★	★	7, poor

TABLE 3 Risk of bias evaluation following Moga et al. (2012)

Study	Selection were the cases adequately described?	Intervention has the intervention been adequately described and has the relevant data been adequately collected?	Outcome has the outcome been adequately described, and the corresponding data adequately collected?	Follow-up was follow-up long enough for outcomes to occur	Total
Neckel et al. (2021)	Yes	Yes	Yes (indirect)	Yes	★★★★
Sandoval et al. (2020)	Yes	No	Yes (indirect)	No	★★
Di Carlo (2019)	Yes	Yes	Yes	Yes	★★★★
Papi (2019)	Yes	Yes	Yes	Yes	★★★★
Curi (2018)	Yes	Yes	Yes	Yes	★★★★
Rana (2016)	Yes	No	Yes	Yes	★★★
Nack (2015)	Yes	Yes	Yes (indirect)	YES	★★★
Buurman (2013)	Yes	No	No (indirect)	Yes	★★
Buddula (2012)	Yes (data matching Buddula 2011)	Yes	Yes	Yes	★★★★
Buddula (2011)	Yes (data matching Buddula 2012)	Yes	Yes	Yes	★★★★
Bodard (2011)	Unclear	Yes	Yes	Yes	★★★
Sammartino (2011)	Yes	Yes	Yes	Yes	★★★★
Heberer 2011 (Nack 2015)	Yes	Yes	Yes (indirect)	Yes	★★★
Cuesta-Gil (2008)	Yes	Yes	Yes	Yes	★★★★
Nelson (2007)	Yes	Yes	Yes	Yes	★★★★
Schoen (2007)	Yes	Yes	Yes	Yes	★★★★
Visch (2002)	Yes	Yes	Yes	Yes	★★★★
Grötz (1999)	Yes	Yes	No/unclear (exclusion of some implant losses)	Yes	★★★
Betz (1999)	Yes	Yes	Yes	Unclear (yes?)	★★★
Niimi (1998)	No	Yes	No/unclear (exclusion of implants placed post RT and implants in irrad. GB)	Yes	★★
Keller (1997)	No	Yes	Yes	Yes	★★★
Esser (1997)	No	Yes	Yes	Yes	★★★
Jisander (1997)	No	Yes	Unclear	Yes	★★(★)
Watzinger (1996)	Yes	Yes	Yes	Yes	★★★★

Neckel et al. (2020) and Pieralli et al. (2021), all patients received a professional implant cleaning every 3 months.

However, this research was faced with limitations that will be addressed now. For instance, most of the included studies were conducted retrospectively, and no prospective randomized studies have been found. Hence, those studies had to deal with different treatment concepts, unequal patient cohorts and sometimes lack of information. Another factor that may negatively impact the validity of the results is the diversity of included studies regarding their purpose, procedure and evaluation. The focus of some studies was not the evaluation of implant survival, which means the study's design and selection of patient cohorts aimed for a different outcome and implant survival was only evaluated indirectly. Furthermore, it was not possible to conduct a multivariate analysis due to missing data on other potential risk factors, for example the age of the patients. In conclusion, it must be taken into account that there is a high risk of bias for this analysis, and the level of evidence of the selected studies is low. Given these points, the results should be considered with caution.

5 | CONCLUSION

Despite all difficulties, dental implants provide a great benefit to oral rehabilitation of cancer patients. Within the limits of the current evaluation and in awareness of possible bias and weak points of the retrospective meta-analytic approach, the present study supports the current recommendation to offer the possibility of implant therapy to head and neck cancer patients. When patients are treated with radiotherapy, the adverse effects of irradiation are negatively influencing the outcome. Therefore, implantation should be carefully considered, taking further risk factors such as smoking into account. The treatment requires precise planning, and a close follow-up care should be established. If possible, the insertion of implants into local bone should be preferred to placement in bone grafts for patients receiving radiotherapy. To summarise, implant restoration can be offered to irradiated head and neck cancer patients after a thorough benefit risk analysis.

AUTHOR CONTRIBUTIONS

Katrin Reinicke: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal).

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CONFLICT OF INTEREST

There are no commercial or other associations that might create a duality of interests in connection with the article. Eik Schiegnitz reports lectures, personal fees and/or grants from Dentsply, Geistlich, Medartis, Septodont and Straumann outside the submitted work. Katrin Reinicke declares that she has no conflict of interest. Keyvan Sagheb reports lectures, personal fees and/or grants from Dentsply, Geistlich, and Straumann outside the submitted work. Jochem König declares that she has no conflict of interest. Bilal Al-Nawas reports lectures, personal fees and/or grants from Camlog, Dentsply, Geistlich, Medartis, Straumann and Zimmer outside the submitted work. Knut A. Grötz reports lectures, personal fees and/or grants from Dentsply, Geistlich, Medartis, Septodont and Straumann outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the result section of this article.

CONSENT FOR PUBLICATION

All authors confirm consent for publication.

AUTHORS' INFORMATION

The data from this study are part of the dissertation work submitted to Johannes Gutenberg University, Mainz, as part of doctoral thesis of Katrin Reinicke.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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